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INTERNATIONAL FORUM

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International Forum on the Management of Major Haemorrhage: Summary

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INTRODUCTION

Acute bleeding that requires large volume transfusions can occur in any clinical setting [1–3]. The optimal management of this type of bleeding is complex and has a major cost burden for health care services [4]. In the last two decades, we have seen an explosion in the number of studies evaluating the role of blood transfusion or alternatives (e.g., haemostatic agents) on clinical outcomes. Studies in trauma have demonstrated that the early and balanced transfusion resuscitation in bleeding patients improve clinical outcomes [5–8]. Delivery of these regimens for transfusion has been supported and enabled by the widespread use of major haemorrhage protocols (MHPs) in hospitals. However, it is unclear how far the results from studies in trauma, where much of the evidence on transfusion management is found, should be extrapolated to other settings of major bleeding. The different findings between results of the large randomized control trials of tranexamic acid use in acquired bleeding (i.e., trauma [9, 10], obstetric [11] and gastrointestinal bleeding) [12] clearly illustrate how a '*one-size-fits-all*' approach may not be suitable across all settings of major bleeding.

The evidence underpinning the role of MHP on the clinical outcome is primarily based on observational studies, rather than interventional trials. However, these protocols have now become a standard of care for most hospitals. For example, the UK national audit of management of major haemorrhage (MH) in 2018 where 166 hospitals–trusts were enrolled and 826 cases were analysed, showed that 99% of hospitals had MHPs in place for managing major bleeding and that the main causes for MH (defined as bleeding that triggers MHP) were surgery, followed by obstetrics, gastrointestinal bleeding and trauma [13]. Considering that these protocols consume a lot of healthcare resources, it is important that there are national and local guidelines to guide clinicians on how to implement these protocols in real life, as well as audit their use on regular basis.

Currently, there is no internationally agreed definition for massive transfusion (MT). The most common definitions used in clinical practice include transfusion of ≥10 red blood cell (RBC) units in 24 h, or ≥6 RBC units in 6 h; or ≥5 RBC units in 4 h [3, 14–16]. Other definitions such as 'ultramassive transfusion', have also been used for patients who are transfused ≥20 RBC over the course of any 2 consecutive calendar days [17]. However, these definitions have limited use in clinical management of patients, as they do not identify (massive) bleeding patients early, and more importantly they are applied retrospectively and often fail to capture patients who die in the first few hours of bleeding, known as 'survivorship bias' [18, 19]. Further, these definitions do not include other blood components (like plasma or platelets), blood products (i.e., haemostatic agents) or fluid volume, all of which are used during the initial resuscitation stage of bleeding.

Management of a massively transfused patient also poses logistical challenges for blood collection centres and hospital transfusion laboratories who need to manage blood stocks to ensure that enough blood is available for all patients who needed it and that the right blood is delivered to the right patients. This is more challenging when special requirements are needed (e.g., RhD negative RBC for women of childbearing potential or unknown patients), or during major incidents when demand for blood may exceed supply. In such

circumstance, the delivery of blood components may require a modified approach, necessitating advanced planning and knowledge of the transfusion service [20].

Recognizing these uncertainties, we designed an International Forum to explore a range of issues related to the processes and management of MH. Questions were asked to seek information on definitions of MH and/or MT, current strategies for transfusion management of bleeding (such as blood component ratios and fibrinogen target) and availability of national guidelines–policies on management of MH. An additional question explored the use of RhD negative RBC for women of childbearing potential or unknown patients, given the ongoing constraints on supply of this type of red cell component by all transfusion services. Respondent demographic data were also captured. A total of 22 sites were invited to participate in the forum and of these 13 responded, representing 13 countries.

SUMMARY OF RESPONSES

Question 1 Respondents' demographics

Of the 13 respondents, 5 were from Asia (India, Indonesia, Israel, Japan and Saudi Arabia), 3 from Europe (Germany, Norway and the United Kingdom), 2 from North and Central America (Canada and United States), 1 from Africa (Nigeria), 1 from Oceania (Australia) and 1 from South America (Chile). All respondents presented their demographic data at the local level (i.e., hospital), except Canada, which presented national-level data (Table 1).

Question 2 Definition of major haemorrhage and/or massive transfusion

Question 2 was divided into four categories, which are reported here as 2a, 2b, 2c and 2d.

Question 2a How do you define major haemorrhage and/or massive transfusion in adults?

Do you have separate definitions for MAJOR TRANSFUSION, MASSIVE TRANSFUSION and SUPRA-MASSIVE TRANSFUSION in adults?

Do these definitions apply to all clinical settings or are there different definitions used for different clinical settings in adults?

Do you think we should use one definition for MAJOR TRANSFUSION, MASSIVE TRANSFUSION and SUPRA-MASSIVE TRANSFUSION for different clinical settings in adults?

The definition of MH and/or MT was answered differently between respondents, with some providing separate definitions for MH and MT, while others either presented one answer for both or provided information only on what triggers the MHP (Table 2). By and large, these definitions applied to all clinical settings, apart from India, Saudi Arabia and Israel who had a separate definition for trauma MH. Germany only presented the definition of MH for the trauma setting.

The most common MT definition used was transfusion of 10 or more RBC units in 24 h. No country had a separate definition for *MAJOR*, *MASSIVE* and *SUPRA-MASSIVE transfusion*. Regarding the need for having one definition for *MAJOR*, *MASSIVE* and *SUPRA-MASSIVE* transfusion for different clinical settings, respondents stated that having a separate definition could be of benefit, especially in the analysis and comparison of data between studies (Australia), helping policymakers to manage blood component inventories (India) or evaluating compliance with the MHP (Saudi Arabia). However, all respondents indicated that in clinical practice having several definitions for large volume transfusions is of limited use, because they are retrospective and do not impact the decision-making process of the acute management of bleeding, and they could introduce complexities and cause confusion among clinical and laboratory teams.

Question 2b In your setting, have you adapted national or other formal guidelines for management of MH and/or MT in adults?

Do you have one main guideline that applies to all clinical settings, or are there different guidelines for different clinical settings (i.e., trauma, cardiothoracic surgery, obstetrics, gastrointestinal bleeding, surgical or medical bleeding, etc.)?

Seven respondents (Australia, Chile, Japan, Nigeria, Norway, Saudi Arabia and the United Kingdom) stated that they have adapted their own national guidelines for management of MH; however, for Norway and Saudi Arabia, this was only for trauma and obstetric settings, respectively. For non-obstetric bleedings, Saudi Arabia used the Australian guidelines, while Germany and Indonesia stated that they have adapted the European guidelines for major trauma haemorrhage [26] and for severe perioperative bleeding [27], respectively. Canada did not have a national guideline, but in 2011, they hosted an MT Consensus Conference to provide detailed guidance for clinicians on this topic [28]. All other countries adapted their own local guidelines.

Australia, Canada, Norway, United Kingdom and United States stated that their guidelines apply to all adult clinical settings, with minor modifications for different specialties, particularly for trauma, obstetric and cardiac surgery. Germany and India stated that they have specific guidelines for trauma, while Israel stated that their guideline is specific to trauma and gastrointestinal bleeding.

Question 2c Do you have clear policies or mechanisms in place for updating and/or renewing guidelines used in clinical practice for management of MH and/or MT in adults? If yes, please describe.

Guidelines are updated every 2 years (Saudi Arabia, United States), or every 3 years (Canada, Chile, Germany, United Kingdom), or sooner if evidence becomes available (Australia, Norway, United Kingdom, United States). Other countries had no policies in updating guidelines.

TABLE 1 Respondent demographics

Country	Type of hospital(s)	Geographic location (city, remote area, regional)	Inpatient bed numbers	RBC units transfused per year
Australia	Academic hospital	Serves the state of Victoria's largest metropolitan public health service	103 beds in private hospital 1850 inpatient beds	22,700
Canada	158 hospitals—of these 150 stock and issue blood components	Large cities, smaller cities and remote rural areas	23,000 inpatient beds	336,282
Chile	Tertiary and teaching hospital	City of Santiago	395 beds	5000 haemocomponents[a]
Germany	Community hospital that serves as a teaching hospital for two universities	Serving a metropolitan area in the Western part of Germany close to Dutch–Belgian border	850–950 beds	5500–7000 blood products[a]
India	Tertiary care academic hospitals	North India: serves smaller hospitals in the capital region, and receives patients from across the nation	2800 beds	75,000–78,000 units
Indonesia	Tertiary and teaching hospital	City of Yogyakarta	820 beds	26,000 units
Israel	University hospital	Urban and rural population	890 inpatient beds 110 outpatient beds	7500–8000 units
Japan	University hospitals—two hospitals (H)	H1—city of Kashihara H2—city of Nagoya	H1—992 inpatient beds H2—2200 outpatients on weekdays and 1085 inpatient beds	H1—12,000 units H2—16,611 units
Nigeria	University hospital	Receives patients from within and outside city of Ibadan	850 inpatient beds 150 outpatient beds	7000–12,000 units of blood[a]
Norway	University hospital	City of Bergen	790 beds	15,000 units
Saudi Arabia	Tertiary academic hospital	City of Jeddah	600 inpatient beds 30 outpatient beds	12,000
United Kingdom	Academic trust that included four hospitals	Three are located in the city of Oxford and one in a town (~40 miles from the city)	1100 beds	17,000 units
United States	Tertiary teaching hospital	City	767	33,000 units

Abbreviations: H, hospital; RBC, red blood cell.
[a]Reported as total blood products and not as red cell units.

Question 2d Has a national, multi-site or hospital-based audit of practice against the guidelines used in clinical practice for management of MH and/or MT in adults been undertaken?
If yes, please provide (1) the clinical setting, (2) the frequency of audit cycle and (3) the name of the organizing body that mandates or co-ordinates the audit.

Of the 13 respondents, 5 stated that they have undertaken audits of MH at a local level for different settings (Australia, Canada, Japan, Norway and the United Kingdom). Only United Kingdom had undertaken a nationwide audit in 2018 and this included all clinical settings in adults [13]. In 2018, a provincial survey of MHP of all hospitals was conducted in Canada across all clinical settings [29]: this showed marked variability, and failed to include the eight key quality metrics deemed necessary in the Ontario MHP, which was made public in 2021 [24]. Canada is planning to conduct an audit in 2022. Australia also stated that they participate in state-wide transfusion audits and other practice improvement activities, however, it was not specified if this included management of MH audits. Other countries answered as 'No' to this question.

Question 3 Blood transfusion management and tranexamic use for MH
Question 3 was also divided into five subquestions. Four subquestions focusing on blood transfusion management are reported below as 3a, 3b, 3c and 3d. Responses to subquestion 3e, focusing on tranexamic use for MH, are summarized separately.

Question 3a What is the RED BLOOD CELLS to PLASMA ratio that your guidelines recommend for management of MH?

Question 3b What is the RED BLOOD CELLS to PLATELETS ratio that your guidelines recommend for management of MH?

Question 3c What is the FIBRINOGEN trigger that your guidelines recommend for administering fibrinogen replacement therapy for management of MH?

TABLE 2 Definition of major haemorrhage and/or massive transfusion in adults

Country	Definitions of major haemorrhage (MH) and/or massive transfusion (MT)
Australia	• MT: - ≥4 RBC units in 4 h, or - Loss or transfusion of one BV over 24 h • More 'real time' definitions include - Replacement of half a BV within 4 h, or - Blood loss of >150 ml/min, or - Receipt of 10 RBC units
Canada	• ABC score (trauma only) • Shock index or resuscitation intensity[a]
Chile	• Haemorrhagic shock as: 'Type IV ATLS haemorrhage, loss ≥2000 cc'
Germany	• MH and/or MT is defined as: - ≥10 RBCs units with 24 h, which corresponds to one complete BV exchange within 24 h • Clinically MH is anticipated in the presence of bleeding with laboratory signs of shock reflected by: - Base excess and lactate, or - Failure to achieve hemodynamic stability despite volume loading in terms of non-responsiveness, or - Need for vasopressor support • In most dynamic scenarios, we use: - 50% volume exchange with 3 h, or - 4 RBC units within 1 h, or - Ongoing blood loss ≥150 ml/min
India	• MH and/or MT for trauma: - ≥4 of RBC units within 1 h • MH and/or MT for other: - ≥10 RBC units within 24 h
Indonesia	• MT: >10 units of RBC in 24 h
Israel	• MH: - Loss of >1 BV within 24 h, or - 50% of the patient's total BV lost in <3 h, or - Bleeding in excess of 150 ml/min • MH in trauma: - Systolic BP <90 mmHg and/or PR >110/min
Japan	• No uniform definition for MH and/or MT[b] • For activating MHP: - We use patient vital signs and hemodynamic instability assessed by shock index, the severity and complexity of bleeding
Nigeria	• MH: - Loss of ≥1 BV within 24 h, or - 50% of total BV lost in <3 h • For PPH, MH: - Blood loss of 1500 ml [21] • MT: - Replacement of the patient's BV with RBCs in 24 h, or - 10 RBC units within 24 h • For early identification of MT: - >5 RBC units within 4 h
Norway [22]	• MT: - ≥5 RBC units within 3 h, or - ≥10 RBC units within 24 h
Saudi Arabia	• MT: - 4 RBC units within 1 h and anticipated need for more, or - Replacement of 50% BV in 4 h, or - Rate of blood loss ≥150 ml/min • For activating MHP in trauma: - ABC score of >2 points[c]
United Kingdom	• MH [23]: - Bleeding, which leads to an HR >110 beats/min and/or systolic BP <90 mmHg - Hospitals must have locally agreed triggers

(Continues)

TABLE 2 (Continued)

Country	Definitions of major haemorrhage (MH) and/or massive transfusion (MT)
United States	• A situation in which a large number of blood products are expected to be transfused in a short amount of time • This may include adult patients who have 8–10 units replaced in 6 h or when the transfused volume equals the patient's total blood volume

Abbreviations: ABC, assessment of blood consumption; ATLS, advanced trauma life support; BP, blood pressure; BV, blood volume; HR, heart rate; MHP, major haemorrhage protocol; PPH, postpartum hemorrhage; PR, pulse rate; RBC, red blood cell.
[a]>4 units of fluid in first 30 min with '1 unit' defined as any of 1 unit RBC, 1 unit plasma, 500 ml colloid or 1 L crystalloid [24].
[b]No uniform definitions because the pathogenesis and mechanisms of coagulopathy vary depending on the clinical settings.
[c]ABC scoring 1 point for each of the following: penetrating mechanism, positive focused assessment sonography for trauma, arrival systolic blood pressure of 90 mmHg or less and arrival heart rate equal to 120 bpm or more [25].

Question 3d Do these ratios and fibrinogen trigger apply to all clinical settings or are there different recommendations for different clinical settings (i.e., trauma, cardiothoracic surgery, obstetrics, gastrointestinal bleeding, surgical or medical bleeding, etc.)?

Results are summarized in Table 3. The most common RBC:FFP ratio used was 1:1 for trauma and 2:1 for non-trauma bleeding. The RBC:platelet ratio varied more, with six responders stating that they had no specific ratio (Australia, Canada, Germany, India, Nigeria and the United Kingdom) and relied on the platelet count at the time of ongoing bleeding (Australia, Canada, Germany and the United Kingdom), four used a 1:1 ratio (Chile, Indonesia, Norway and Saudi Arabia) and others had different ratios for different clinical settings (Japan) or used the point of care testing to determine the need for platelet transfusion (Israel).

As far as the fibrinogen replacement therapy is concerned (Table 3), this was initiated if fibrinogen level was <2.0 g/L for postpartum haemorrhage or <1.5 g/L for other bleeding (Australia, Canada, Japan, Saudi Arabia and the United Kingdom), two respondents stated that they had no fibrinogen trigger (Nigeria and Indonesia), two had a trigger for trauma, but not for other settings (India and Norway) and two used one fibrinogen trigger for all settings (Chile and United States).

Question 3e Do your guidelines recommend the use of tranexamic acid for management of MH? Do these recommendations apply to all clinical settings or are there different recommendations for different clinical settings (i.e., trauma, cardiothoracic surgery, obstetrics, gastrointestinal bleeding, surgical or medical bleeding, etc.)?

Respondents from Chile, Indonesia, Nigeria and the United States stated that tranexamic acid is not in their guidelines–policies, Germany and Norway only recommended it for trauma, while other countries recommended it for all settings (Australia, Canada, India, Israel, Japan, Saudi Arabia and the United Kingdom). The respondent from Japan stated that the recommendation for administering tranexamic acid to trauma and obstetric patients who exhibit massive bleeding or are at risk of significant haemorrhage, is weak, while United Kingdom and Canada contraindicated the use of tranexamic acid in gastrointestinal bleeding following the recent publication of the HALT-IT trial [12].

Question 4 Resource utilization

Question 4a In the setting of MH, do you use group O RhD positive RBCs or Group O RhD negative RBCs for all adult patients who have unknown blood group or does your product selection differ based on patient age and/or gender?

The answers to this question are divided into five categories: (1) group O RhD negative is transfused to females of childbearing potential only (Canada, India, Israel, United Kingdom and United States); (2) group O RhD negative is provided to all patients regardless of age and sex (Australia, Chile and Saudi Arabia); (3) group O RhD negative is transfused to females of childbearing potential and children (Germany, Nigeria); (4) group O RhD positive is transfused to all patients as the prevalence of group O RhD negative in the population is very low (Japan and Indonesia) and (5) group O RhD positive whole blood or RBC is transfused to males and females older than 50 years (Norway).

Question 4b In the setting of MH, do you have a policy in your institution for when to switch RhD negative women of childbearing potential or children to RhD positive RBCs when RhD negative inventory is limited and the patient is requiring significant transfusion support such that the supply for the rest of the hospital becomes threatened?

Apart from Chile, and excluding responses from Japan and Indonesia where group O RhD positive RBC are used for all patients, others stated that they do not have a policy in place to cover this eventuality; however, all respondents stated that they will switch to group O RhD positive or group-specific RBCs, if supply for group O RhD negative is lower than demand.

Question 4c In the setting of MH, do you have a 'shortage' policy in your institution for when to discontinue RBC transfusion support when inventory is limited and the patient is requiring significant transfusion support such that the supply for the rest of the hospital might become threatened or limited? For example, in the early stages of the COVID pandemic when there were concerns about donations and blood supply, did your hospital develop such a policy in the event of a severe blood shortage?

TABLE 3 Blood component ratios

Country	RBC:FFP ratio	RBC:PLT ratio	Fibrinogen trigger
Australia	2:1 for all[a]	No ratio[b] Maintain count >50 × 10^9/L, maintain count >100 × 10^9/L for head injury	<2.0 g/L for PPH <1.5 g/L for others
Canada	2:1 for all	No ratio Maintain count >50 × 10^9/L, maintain count >100 × 10^9/L for intracranial or spinal injury	<2.0 g/L for PPH <1.5 g/L for others
Chile	1:1 for all	1:1 for all[c]	≤80 mg/dl for all
Germany	1:1 for trauma 2:1 for others	No ratio 4:1 for trauma Maintain count >50 × 10^9/L or guided by ROTEM	<1.5 g/L, or if FIBTEM is abnormal
India	1:1 for trauma No recommendation for others	1:1 for trauma No pre-defined ratio for others	<1.5 g/L for trauma No trigger for others
Indonesia	1:1 for all[d]	1:1 for all[d]	No trigger
Israel	*1:1 for all*	Guided by TEG[e]	Guided by TEG[e]
Japan	1:1 and minimally at >1:1 for trauma >1:1 for cardiac, obstetric No recommendation for others	1:1 and minimally at >1:2 for trauma 1:1 cardiac Others no recommendation	150–200 mg/dl for PPH <150 mg/dl for trauma <150 mg/dl for cardiac
Nigeria[f]	5:1 for PPH No recommendation for others	No recommendation	No recommendation
Norway	1:1 if whole blood is not available	1:1 if whole blood is not available	<2 g/L for trauma No trigger for others
Saudi Arabia	2:1 for all	1:1 for all	<2.0 g/L for PPH <1.5 g/L for others
United Kingdom	1:1 for trauma 2:1 for other setting[a]	No ratio Maintain platelet count >50 × 10^9/L: to achieve platelet are requested if count <100 × 10^9/L	<2.0 g/L for PPH <1.5 g/L for others
United States	1:1 for all	6 to 1 apheresis	<100 mg/dl for all

Abbreviations: aPTT, activated partial thromboplastin time; FFP, fresh frozen plasma; FIBTEM, fibrin-based extrinsically activated test with tissue factor and the platelet inhibitor cytochalasin D; INR, international normalized ratio; PLT, platelet; PPH, postpartum hemorrhage; RBC, red blood cell; ROTEM, rotational thromboelastometry; TEG, thromboelastography.

[a]Adjust further FFP to maintain INR and aPTT to <1.5× normal.

[b]First round of blood products includes a 4:1 ratio and second round does not include platelets.

[c]1 unit of RBC per 1 apheresis platelet concentrate or platelet pool with the number of units corresponding to 1 unit per 10 kilos.

[d]This setting is not yet being a hospital policy but is particularly applied to cardiothoracic surgery when an order of 5 red blood cells and 5 platelets is usually made.

[e]A pool of 5 platelet units and fibrinogen replacement is given as part of the second pack of components.

[f]Use whole blood.

Of the 13 respondents, 5 had a 'shortage' policy in place (Australia, Canada, Norway, Saudi Arabia, United Kingdom), while others did not (Chile, India, Germany, Israel, Nigeria). The respondent from the United States stated that they have a policy to review cases and consult with the clinical provider when RBC transfusion exceeds 100 units per patient, which could jeopardize the overall inventory. Most responders stated that if there is a blood shortage, they will postpone elective surgeries and review all emergency transfusion requests by a transfusion specialist. In the early stage of the COVID-19 pandemic, Norway implemented cold-stored apheresis platelet concentrates to mitigate the risk of insufficient platelet inventory for bleeding patients.

CONCLUSION

Treatment of MH that results in large volumes of allogeneic blood transfusion is associated with significant morbidity and mortality and costs burden for health care services [4]. This international survey showed a huge variation in the definition of MH and/or MT between countries, with most countries using the same definitions for all clinical settings. There was no country that categorized large volume transfusions into MAJOR, MASSIVE or SUPRA-MASSIVE transfusion. Respondents indicated that different large volume definitions may be important to compare data between studies–services and help policymakers to manage blood stocks, but they all specified that these definitions are not useful in clinical practice, as they do not impact on the decision-making process of the acute management of bleeding patients, and they could potentially introduce complexities and confusion for clinical and laboratory staff.

Only seven countries had a national guideline–policy in place on how to manage major bleeding with other countries using other nation's guidelines or developing their own policy. For trauma and obstetrics, the guidance on the RBC:FFP ratio and fibrinogen trigger, respectively, were clearly defined in most protocols, while for other major bleeding settings the 2:1 ratio of RBC:FFP and fibrinogen of <1.5 g/L were the most common

approaches for non-trauma bleeding for most countries. These results are not at all surprising, considering the lack of evidence in this field.

The evidence on the use of tranexamic acid for treatment of major bleeding relating to trauma, surgery, obstetrics and gastrointestinal causes, is stronger [9, 10, 12, 30] than blood transfusion ratios or fibrinogen triggers. Despite this, our results showed a diverse response on the use of tranexamic acid even for settings where there is some evidence. We believe that integrating tranexamic acid into the MHP will ensure that it is administered to all patients who need it, but this may also lead to some patients receiving it when it may be contraindicated, such as gastrointestinal bleeding.

The answer around resource utilization for the use of universal RBC group and the availability of '*blood shortage plan*' for red cells for management of bleeding also varied significantly between countries. For countries that have a low prevalence of group O RhD negative donors resource utilization of RhD negative RBC units is not an issue, however, for others this is a problem, as the demand for this resource rises to treat trauma patients who are bleeding outside the hospital setting [31–34]. Therefore, an individual risk assessment from each country is required to better understand the wider implications (for both patients and healthcare providers) of continuing to support all unknown patients with RhD negative red cell containing components and more research is needed to look at innovative technologies to develop universal blood components [35], so that we can improve overall blood component inventory.

In conclusion, among the respondents to this forum, there was wide variation on the definition of MH and MT as well as transfusion management of acquired MH. This suggests a need for the international blood transfusion community to provide further guidance in this field, so that we can harmonize treatment of bleeding disorders and research, with improved outcomes for patients and healthcare systems.

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